NKDEP
National Kidney Disease Education Program

Creatinine Standardization Program

Recommendations for IVD Manufacturers*

The National Kidney Disease Education Program (NKDEP), in collaboration with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the European Communities Confederation of Clinical Chemistry (EC4), has launched the Creatinine Standardization Program to reduce inter-laboratory variation in creatinine assay calibration and provide more accurate estimates of glomerular filtration rate (GFR). The effort is part of a larger NKDEP initiative to help healthcare providers better identify and treat chronic kidney disease in order to prevent or delay kidney failure and improve patient outcomes.

IVD manufacturers are crucial partners in the successful implementation of this program. The following steps are necessary to ensure a smooth transition from traditional calibration of routine creatinine methods to calibration that is traceable to an isotope dilution mass spectrometry (IDMS) reference method:

1) Continue using or recommending the original Modification of Diet in Renal Disease (MDRD) Study equation for routine methods that have not been calibrated to be traceable to IDMS.
2) Calibrate serum creatinine methods to be traceable to an IDMS reference measurement procedure. Standardization of method calibration will reduce the inter-laboratory bias in results and yield more accurate estimated GFR (eGFR) using the IDMS-traceable MDRD Study equation.
    - A new reference material with IDMS-traceable creatinine values (NIST SRM 967) will be available in mid-2006 for use in calibrating routine methods.
    - Alternatively, routine methods can be calibrated with the assistance of an existing IDMS reference measurement laboratory. The Joint Committee for Traceability in Laboratory Medicine (JCTLM) lists approved reference measurement procedures and the submitting laboratories at www.bipm.fr/utils/en/xls/jctlm_listI.xls. In 2007, JCTLM intends to provide a list of laboratories that can provide reference measurement services.
3) Coordinate with customer laboratories so that, upon using a method with IDMS-traceable calibration, they immediately begin using the IDMS-traceable MDRD Study equation to estimate GFR. During the transition to IDMS-traceable calibration, methods that produce results that have acceptable bias [as defined in *Clinical Chemistry* 2006;52(1):5-18] when compared to an IDMS-traceable method should use the IDMS-traceable MDRD Study equation.
4) Collaborate with the NKDEP and other professional organizations to communicate to customers about the clinical issues associated with introducing a serum creatinine method that is calibrated to be traceable to IDMS. IVD manufacturers should:
    - Provide a serum creatinine reference interval appropriate for the method.
        - Creatinine clearance values based on measured serum and urine creatinine results may increase and a new reference interval and interpretive criteria may need to be established. The effect on measured creatinine clearance will vary depending on the procedure used to calibrate serum and urine measurements.

* These recommendations update those originally published in *Clinical Chemistry* 2006;52(1):5-18.

- For most patients, an eGFR using the MDRD Study equation is more accurate than a creatinine clearance calculated from serum and urine measurements. Therefore, NKDEP recommends not performing a measured creatinine clearance procedure for adults except when the patient's basal creatinine production is very abnormal. This may be the case with patients of extreme body size or muscle mass (e.g., obese, severely malnourished, amputees, paraplegics or other muscle-wasting diseases) or with unusual dietary intake (e.g., vegetarian, creatine supplements).

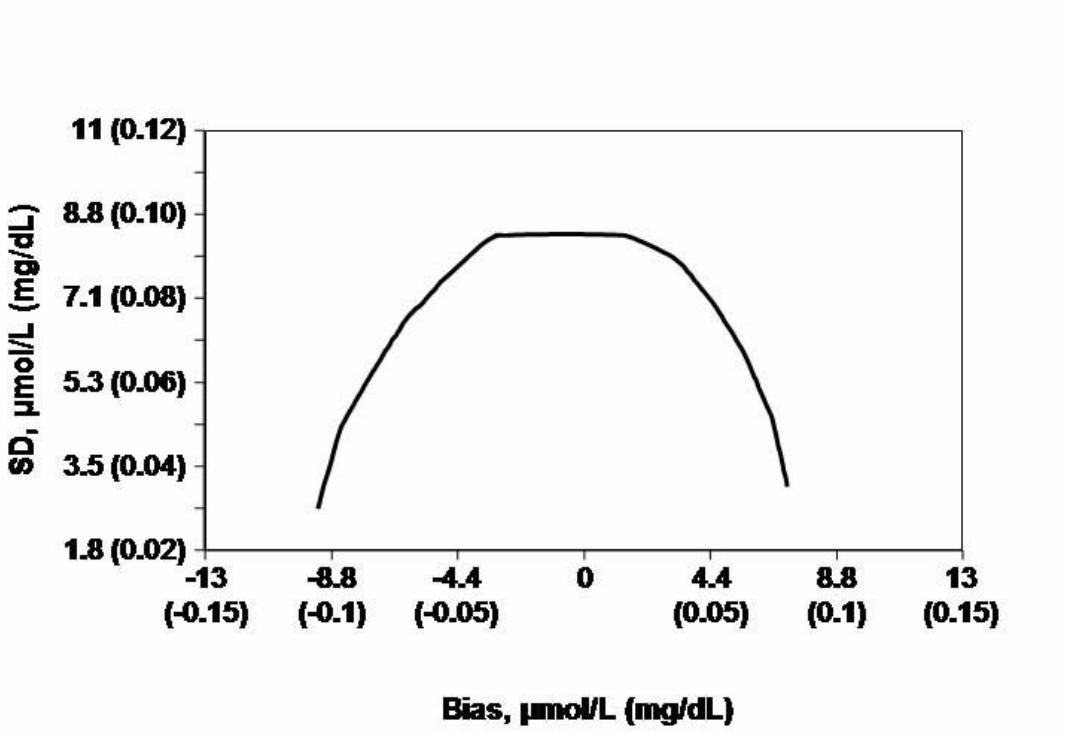
- Provide information to clinical laboratories describing the relationship between creatinine results when measured with methods that have IDMS-traceable calibration compared to the results obtained using methods with traditional calibration. Manufacturers should provide detailed descriptions (including mathematical conversion factors, equations, or functions) of the impact of their calibration changes, for both serum and urine creatinine values, with emphasis on the 0.5 to 2.5 mg/dL (45 to 220 µmol/L) range of interest. This will ensure that customers or laboratories who are using any of the pharmacy drug dosing approaches can adjust IDMS-traceable creatinine values for use with appropriate legacy dosing reference tables and algorithms (such as serum creatinine value; GFR or creatinine clearance based on estimating equations other than the MDRD Study equation; or traditionally measured creatinine clearance from serum and urine values).

    - The clinical laboratory should notify the pharmacy and drug prescribers to inform them of the expected magnitude of change in serum creatinine values, compared to the previous traditionally calibrated method, and whether the creatinine clearance measured from serum and urine will be affected by the change. Serum creatinine and algorithms to estimate kidney function are used to adjust the doses of drugs. Creatinine methods with calibration traceable to IDMS may have large enough changes in creatinine values that the drug dose algorithms will be affected. For additional information refer to the *Recommendations for Pharmacists and Authorized Drug Prescribers* available at www.nkdep.nih.gov/labprofessionals.

- Following implementation of serum creatinine methods with calibration traceable to IDMS, other equations used to estimate kidney function such as Cockcroft-Gault, Schwartz, or Counahan-Barratt will give values that, in most cases, are higher than the values obtained using traditionally calibrated creatinine methods. This change will affect interpretive criteria based on these estimates of kidney function.

- Creatinine measurements at the low values usually observed in pediatric patients have a greater measurement variability than for values seen in adults. Estimates of kidney function based on these values also will have greater variability than for adults.

5) Precision of creatinine methods should be improved to meet the total error goal for serum creatinine measurement described by Figure 3 in the paper published in *Clinical Chemistry* 2006;52(1):5-18. (This is reproduced in the figure below.) This figure provides an error budget for creatinine measurement in the range 1.00-1.50 mg/dL (88.4-133 µmol/L) that will ensure less than 10% increase in the relative error of the eGFR. An example of method performance that would achieve this total error goal is analytical imprecision (including inter-laboratory calibration variability) SD <0.08 mg/dL (7.1 µmol/L) and analytical bias (compared to an IDMS reference measurement procedure) <0.05 mg/dL (4.4 µmol/L) at a serum creatinine concentration of 1.00 mg/dL (88.4 µmol/L).



6) Ensure optimal method performance at 1.00 mg/dL (88.4 µmol/L) for existing and new methods, and ensure that comparable trueness and imprecision extend throughout the analytical measurement range. Method imprecision at concentrations <1.00 mg/dL (88.4 µmol/L) should be addressed to reduce the uncertainty in eGFR for pediatric populations, and possibly to allow extension of eGFR to values >60 mL/min/1.73 m^2.
7) Instruments should report serum creatinine values as mg/dL to two decimal places, or as µmol/L to the nearest whole number, to reduce the contribution of rounding error when using the MDRD Study equation.
8) Address analytical non-specificity issues in routine serum creatinine methods.
9) Communicate with Proficiency Testing and External Quality Assessment Scheme (PT/EQAS) providers to inform them when a revised creatinine calibration will become effective, and work with the PT/EQAS provider to develop appropriate instrument/method peer groups for participants to be evaluated appropriately.
10) The College of American Pathologists' LN24 Survey (commutability validation pending), or comparable EQA with commutable samples and IDMS target values, may be useful to monitor field performance of routine methods.

More information about the Creatinine Standardization Program and recommendations for other groups, including clinical laboratories, are available at www.nkdep.nih.gov/labprofessionals.

Contact Information

For assistance, please contact us at csp@info.niddk.nih.gov or call 301-435-8116.

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